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BREEDING MEDICINAL PLANTS.*

By F. A. Miller, B.S.

The products from medicinal plants are without doubt as valuable to mankind as those from the cereal, vegetable, fruit, flower, fibre and other economic plants under cultivation. The latter have all yielded to the principles of plant breeding, and have supplied man with a wealth and variety of products which nature's laboratory has never equalled. Why should not medicinal plants yield and produce in a similar manner, and through cultivation and improvement be made to furnish mankind with more efficient remedies against disease?

An examination of the crude vegetable drugs as they occur on the drug markets of to-day reveals a mass of inferior materials far in excess of what might be expected. Much of this material is unfit for manufacturing purposes, through adulteration with unknown and worthless admixtures, partial or complete substitution of one plant or plant part for another, old, inert, mouldy drugs which may have been stored under adverse conditions or collected out of season and improperly cured and packed. All this is due to a lack of power to control the production of crude vegetable drugs. Too much must be left to nature or to none too well informed collectors. The faults and inefficiencies of nature need little comment. A comparison of a few improved varieties with their wild ancestors is sufficient evidence that nature is poorly equipped for the production of improved strains.

Ignorant collectors many times are a menace. Personal experience with many of them has revealed an absence of any sense

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of responsibility, and but little power of discrimination in selecting and identifying plants. They cannot separate closely related species, a procedure often necessary in the intelligent collection of medicinal plants, and frankly refuse to observe certain rules governing collection and curing. It is thus evident that the variations of nature associated with ignorance, often give the pharmacist and practicing physician a poor and suspicious product. Rigid inspections must be enforced at all stages in the process of manufacturing medicinal preparations. But however rigid these inspections may be, they cannot overcome all the variations of plant growth or correct all the mistakes of careless collectors. The supply of medicinal plant products should be controlled with the same degree of nicety as the agricultural products or even with greater precision, since in many instances a life is dependent upon the strength and purity of some vegetable drug.

Plant breeders are supplying fruits of varying acid values, corn of high and low percentage of oil and protein, carefully selected sugar beets of high yielding power, and varieties of tobacco suitable for various purposes according to an indicated nicotine content. All of these achievements and numerous others are noteworthy. Of a different character, but of no less importance are the drug producing plants which yield the alkaloids, glucosides, saponins, resins, oleoresins, etc., upon which their curative property depends. Cannot the plants yielding these so-called active principles be brought under the influence and control of the breeder, and be made to produce their respective products more abundantly and more consistently than in the wild state? In attempting to answer this question, experiments have been started with several medicinal plants which will extend over a considerable period of time, and involve various problems of selection and breeding.

The *Solanaceæ* offer as rich a field in the development of improved medicinal forms as it has already offered in the production of the potato, tomato, egg plant and capsicum among the food producing plants, and the datura, solanum, capsicum and tobacco of the decorative forms. In the terminology of the druggist there is found within the same family the very important form, belladonna, henbane and stramonium, all yielding alkaloids and readily amenable to chemical methods of assay. These three genera, in addition to others from different plant families, are

being used in the above mentioned experiments. Chemical and biological methods are being used in checking and following the progress of the work. It is hoped that correlations may be found to exist between high potency and certain morphological characters. This would eliminate in part at least the chemical and physiological assays, which are expensive, and somewhat long. Following is a brief discussion of what is being done with some of the forms under investigation.

BELLADONNA.

Both the leaves and roots of belladonna (*Atropa belladonna*) are used. They must yield respectively 0.30 per cent. and 0.45 per cent. of alkaloids. During the past three years, 6 per cent. of all shipments of the leaf examined were below standard. The variation in percentage of alkaloids for the same period of time was from 0.23 to 0.62 per cent., average 0.43 per cent. Of the shipments of root examined, 28 per cent. were below standard, with a variation of from 0.17 to 0.66 per cent., average 0.48 per cent. No attempts have been made to breed belladonna for a high yield of alkaloids, a possibility which is suggested by the range of variations as indicated above. That the belladonna plant does possess a higher yielding power than average figures would suggest, is shown by a yield of 0.9 per cent. of alkaloids which was obtained upon a plot fertilized with commercial acid phosphate. Such a high yielding power as this would of course not be transmitted by these plants to their offsprings. It is only mentioned to indicate the possibilities of locating high yielding plants by testing leaves from selected individuals.

During the past summer a number of such selections were made. Individual plants were selected, numbered and inbred. Samples of leaves were taken from these individuals upon which to determine the alkaloidal yield. These selected plants were also propagated vegetatively and the resulting plants are being grown in the greenhouse. Some of them are growing in pots in the original soil in which the parent plants were grown, while others are growing in various mixtures of widely differing soils. In this manner it is hoped that some information may be gained upon the behavior of the alkaloids with respect to inheritance, effects of soils, variation in yield from plants grown from open pollinated and close fertilized seeds, and from those propagated by cuttings.

The selected plants so far tested indicate a variation in yield of from 0.55 per cent. to 0.87 per cent. of alkaloids. The progeny of these plants of known yield will be tested in a similar manner.

The external characters of the belladonna plant are extremely uniform, with the exception of total yield of leaves and roots per plant. This exception will be taken advantage of in selecting for increased production of these products. Individuals vary in amount

FIG. 1.

Commercial test plot of Belladonna.

of dry root produced from 139 grams to 203 grams. It has been stated that the percentage of alkaloids in the roots of this plant increase markedly after the first year, and reach a maximum at the end of the third year's growth. Belladonna is not perfectly hardy throughout the central United States, and more hardy strains must be developed before the above condition can be observed to advantage. Sixteen hundred plants are now being tested

in the vicinity of Indianapolis for relative hardiness. See Figure I for test plot of belladonna.

HENBANE.

Henbane is a pharmacopœial drug, supposed to consist of the dried leaves and flowering tops of *Hyoscyamus niger* collected from plants of the second year's growth. This product must yield not less than 0.08 per cent. of alkaloids. Records covering one hundred and two inspections of this drug purchased in the drug markets of the United States, show but thirteen per cent. with a yield of alkaloids equal to or above this requirement. The remaining eighty-seven per cent. vary from 0.018 per cent. to 0.075 per cent. From a botanical point of view, this drug is also far from uniform. Many samples and shipments contain seeds which germinate readily, and when grown to maturity, furnish a means of accurately identifying the original material. A number of shipments have been checked in this manner during the past two years, and annual plants have been found in nearly all cases. The official requirements state definitely that the drug must be collected from plants of the second year's growth. However, without some provision for controlling this collection, little can be done toward obtaining an official product in this respect. Certainly the above conditions of alkaloidal yield and botanical origin of this drug are strongly suggestive of the necessity and desirability of subjecting the genus to a thorough and rigid investigation. This investigation should have to do with the isolation and cultivation of the annual and biennial forms, as well as all species and varieties of these. Individual plants should be selected for breeding purposes, and tested for yielding properties in the same manner as described for belladonna.

STRAMONIUM.

Stramonium has been taken up in a similar manner, and the work on *Datura stramonium* and *Datura tatula,* two common forms, has now been carried through the second year. Selections of *Datura tatula* gave a variation in alkaloidal percentage of from 0.47 to 0.65. The plants yielding these extremes produced offsprings as follows:

Of ten individuals from the plant yielding 0.47 per cent. alkaloids, a range of from 0.44 per cent. to 0.57 per cent. was obtained,

the average for the ten being 0.51 per cent. Of the same number of individuals from the plant yielding 0.65 per cent., a range of from 0.43 per cent. to 0.77 per cent. was obtained, the average in this case being 0.65 per cent. In the first group seven of the ten plants tested exceeded the parent in alkaloidal yield, while in the second, only five exceeded the parent. It is of interest to note that the lowest limit (0.43 per cent.) was found in the progeny

FIG. II.

Breeding plot of Stramonium.

of the high yielding plant (0.65 per cent.), the lowest limit in that of the low yielding plant (0.47 per cent.) being 0.44 per cent. The most promising feature of this experiment in its present stage is the greater average yield obtained over that from wild plants from the same locality. A mixed sample of leaves from uncultivated plants of *Datura tatula* gave a yield of only 0.35 per cent. in comparison with average yields of 0.51 and 0.65 per cent. from selected plants. These latter figures might also be compared with

the average yield of commercial shipments of stramonium as noted for three years, which is 0.34 per cent. The analysis of the *Datura stramonium* selections of the past year, which were performed in the same manner as those of *Datura tatula,* have not been completed. The parent plants, however, from which these selections were made, gave yields of 0.46 per cent. and 0.55 per cent. respectively, which figures represent the low and high limits obtained from a number of individuals.

Two other varieties of stramonium not common to this country were grown and tested. These were *Datura humulis flava,* bearing large, beautiful, double yellow flowers of peculiar fragrance, and *Datura ferox,* a form very closely resembling *Datura tatula,* but having a more vigorous and robust habit. Both of these forms were obtained from Germany. The first contained in a mixed sample, 0.42 per cent. of alkaloids, and individual selections of the second gave a variation of from 0.53 per cent. to 0.70 per cent. of alkaloids.

It is to be regretted that none of the first plants selected for testing were close fertilized. During the past year, all selected plants were inbred, and only these will be used in continuing the work. Twenty crosses were made among the three species, stramonium, tatula and ferox. The effects of these crosses upon alkaloidal yield as well as upon visible characters, will be noted during the next growing season. See Figure II for breeding plot of stramonium.

DIGITALIS (Foxglove).

Digitalis, the common garden foxglove, has been chosen as another medicinal plant upon which to test the effects of breeding. It is also an official drug, and must consist of the leaves from the second year plant of *Digitalis purpurea* at the commencement of flowering. This form has been included for experimental purposes on account of its value to the physician and because of a wide variation and much uncertainty in physiological effect. There is also a lack of experimental data upon such questions as the comparative value of the wild and cultivated plant and of the many different species and varieties, of the effects of cultivation upon medicinal value, time of collection, methods of curing, packing and storing and of the influence of various ecological factors.

In the study of the group, it is not only desirous to compare

the many species and varieties medicinally, but also to determine their relative yield of crude material, ease of culture, hardiness, flowering period and effects of hybridization upon these respective characters.

Thirty-two forms (see Figure III) consisting of both species and varieties, are under observation. These have been started

FIG. III.

Various species and varieties of Digitalis.

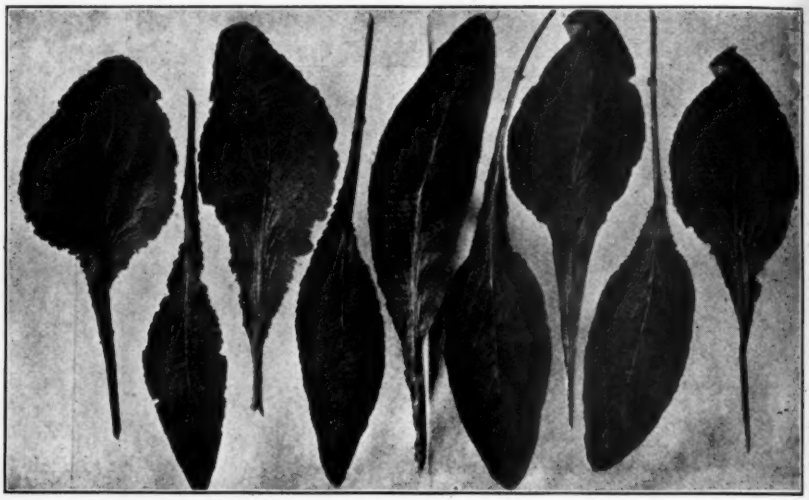
from seed purchased of commercial seedsmen. The most prominent trade catalogues from this country, England, Germany and Japan have been examined, and all forms of the foxglove listed in them have been obtained. Some of these were started in the greenhouse as early as December in an effort to bring as many of them as possible into flower the first year. The following table shows the date planted, number of plants in flower on given dates, and total number of plants, both flowering and non-flowering, at end of growing season:

DATES OF FLOWERING AND NUMBER OF PLANTS IN FLOWER.

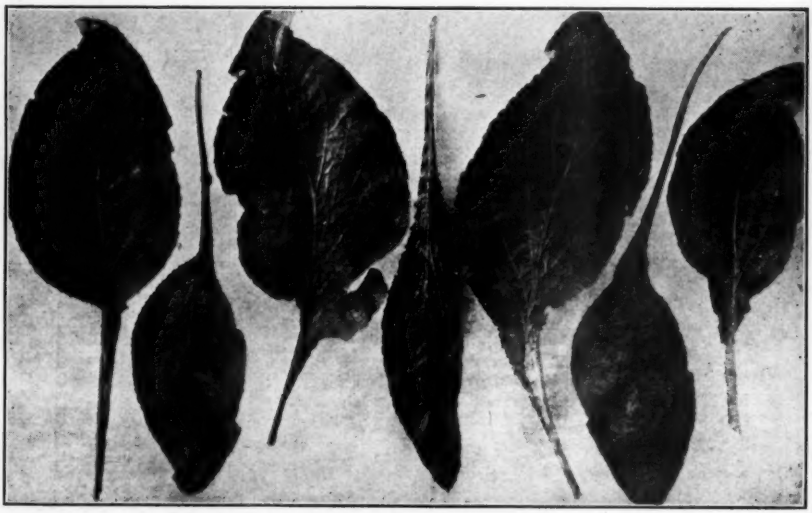
Variety.	Source.	Date Planted.	July 15.	July 20.	July 25.	July 30.	Aug. 10.	Aug. 20.	Sept. 1.	Sept. 20.	Oct. 15.	Number Plants Used.
Digitalis lanata...	Horsford, Vt.	12/20–11	..	..	..	..	..	1	...	2	2	97
Digitalis ambigua..	Horsford, Vt.	12/21–11	1	17	35	49	54	87	151	217	220	233
Digitalis canariensis.....	Watkins & Simpson, London	1/4 –12	..	..	..	..	..	..	..	..	2	224
Digitalis gloxiniæflora lutea.....	Boddington, N. Y.	1/30–12	..	1	1	..	..	3	11	68	95	386
Digitalis purpurea rosea.....	Boddington, N. Y.	2/ 6–12	..	..	..	..	..	1	..	..	..	358
Digitalis purpurea alba.....	Boddington, N. Y.	2/ 6–12	..	..	..	..	1	..	..	..	..	334
Digitalis gloxinioides.....	Horsford, Vt.	2/ 7–12	..	..	..	..	4	..	5	9	10	383
Digitalis monstrosa	Watkins & Simpson, London	2/ 7–12	..	..	..	..	1	2	..	..	2	349
Digitalis grandiflora.....	Dreer, Philadelphia	2/ 7–12	..	1	2	..	5	32	113	189	239	240
Digitalis sibirica...	Horsford, Vt.	2/ 8–12	..	..	..	..	..	..	..	6	20	294
Digitalis ivery's spotted.....	Ferry, Mich.	2/29–12	..	..	..	..	..	..	..	..	1	244
Digitalis sp.....	Yokohama, Japan	3/ 5–12	..	..	..	..	..	..	..	..	5	239
Digitalis macranthus.....	Benary, Germany	3/22–12	..	2	3	..	16	81	161	217	222	231
Digitalis lutea....	Benary, Germany	3/22–12	..	..	..	..	..	..	..	1	3	256
Digitalis buxbaumi	Benary, Germany	3/22–12	..	..	..	..	..	..	1	7	25	319

FIG. IV.

LEAF VARIATIONS IN DIFFERENT PLANTS OF THE SAME SPECIES OR VARIETY. A TYPICAL MATURE LEAF WAS COLLECTED FROM EACH PLANT.



Digitalis purpurea. Watkins and Simpson, London.



Digitalis gloxinioides. Horsford's Nurseries, Vt.

The early flowering individuals noted in the table are being utilized for breeding purposes, in the hope of obtaining either annuals or biennials of a higher and more uniform quality. Mixed samples of leaves collected from plants of the first year's growth of all varieties studied have been biologically tested. Many of the varieties test equally as high as good commercial drug, and some of them even exceed this article in relative strength, as indicated by the above method. Others have proven extremely inactive, the poorest, as indicated by the physiological tests, being only one-sixth as active as the best.

In addition to the biological tests, the external characters must also be closely observed. Upon a basis of leaf forms, the genus is easily divided into two groups. One of these is characterized by broad, rough leaves and includes such varieties as purpurea, monstrosa, alba, gloxinioides and others. They vary greatly in physical characters, and apparently hybridize with considerable ease. The other group is characterized by narrow, smooth leaves and includes such forms as *lanata, ambigua, grandiflora, sibirica, canariensis* and others. The members of this group vary little in external characters, and hybridize with considerable difficulty.

The diversity of leaf forms, as noted for individuals of the same species or variety, is indicated for two forms, in Figure IV. Each leaf was taken from a different plant. The variations in size, shape, margin, petiole, surface and color seem too great and diversified to be explained as individual variabilities. Breeding and the examination of a large number of plants will evidently clear up this point.

The foregoing is only expected to serve as a suggestion to those who may be interested or have the opportunity to observe or investigate medicinal plants. Much good will have resulted if better crude drugs of vegetable origin can be produced from the wild forms, by an application of the rapidly advancing views of the practical breeder. It is only just that the demands upon the plant kingdom should be exhausting, and such will not be the case until medicinal plants are included in the category of the plant breeder.

Botanical Department, ELI LILLY & COMPANY,
Indianapolis, Indiana, January 18, 1913.

MAGMA MAGNESIÆ.[1]

By George M. Beringer.

The National Formulary directs that Magnesia Magma, commonly called Milk of Magnesia, be made by pouring a filtered solution of 81 Gm. of Sodium Hydroxide in 4000 cc. of Water into a filtered solution of 250 Gm. of Magnesium Sulphate in 4000 cc. of Water. The precipitate is washed by decantation, then drained and mixed with sufficient water to make the product measure 1000 cc.

This looks like an exceedingly simple formula that should yield a satisfactory preparation. However, in my experience, it has not proven so, and several modifications are necessary and are included in the improved formula now presented.

The author of the N. F. formula aimed to obtain a very fine precipitate by using very dilute solutions and precipitating at room temperature. He succeeded in doing this, but the precipitate is so light and commonly so bulky that it is with difficulty that it can be reduced to a volume of 1000 cc. and remain sufficiently fluid to pour. The resulting magma usually resembles thick starch paste.

An examination of the wash water shows that the Magnesium is not all precipitated. This is readily understood when the formula is critically examined. The quantity of Sodium Hydroxide directed, 81 Gm., is shown by calculation to be the theoretical amount of pure anhydrous Sodium Hydroxide that would be required to react with 250 Gm. of Magnesium Sulphate, U. S. P., but as Sodium Hydroxide, U. S. P. contains about 90 per cent. pure NaHO, it is self-evident that the formula directs an insufficient amount.

The chemist has been taught the difficulty of completely precipitating Magnesium Hydroxide in the presence of alkaline chlorides or sulphates and that an excess of the solution of potassa or solution of soda is necessary and that "the separation of this precipitate is greatly promoted by boiling the mixture." The present N. F. formula has insufficient alkali instead of an excess,

[1] Read at the annual meeting of the New Jersey Pharmaceutical Association, June 11, 1913.

and, moreover, commits a manipulative error in directing that the Sodium Hydroxide solution be poured into the solution Magnesium Sulphate so that at no time is an excess of alkali present. The use of hot solutions instead of cold should also be directed.

To correct these defects, the following improved formula is presented:

MAGMA MAGNESIÆ.

Magnesium Sulphate	250 Gm.
Sodium Hydroxide	100 Gm.
Water, a sufficient quantity.	

Dissolve the Sodium Hydroxide in 1000 cc. of Water and the Magnesium Sulphate in another portion of 1000 cc. of Water and filter the solutions. Heat the solutions to boiling and add the Magnesium Sulphate to the solution of Sodium Hydroxide with constant stirring. Boil the mixture for fifteen minutes, then remove from the fire and wash several times by decantation and then on a close muslin strainer until the washings are free from saline taste and give not more than a slight turbidity with Barium Chloride T.S. Allow the magma to drain, then transfer to a suitable vessel and add sufficient water to make 1000 cc. and mix thoroughly.

In order to obtain a nice white and smooth preparation, one must be careful of the character of the water used. If distilled water is produced in abundance and at a minimum cost it can be used to advantage. The cost of distilled water to the average pharmacist, however, would preclude its use for the washing of this preparation. Satisfactory water can be cheaply and readily obtained by adding 5 Gm. of powdered Magnesium Carbonate to each litre, boiling and then filtering.

ELIXIR FERRI, QUININÆ ET STRYCHNINÆ PHOSPHATUM.[1]

BY GEORGE M. BERINGER.

The formula for the Elixir of the Phosphates of Iron, Quinine and Strychnine, U. S. P. VIII, has been criticized largely because of the uncertainty of the color in different lots and the rapid

[1] Read at the annual meeting of the New Jersey Pharmaceutical Association, June 11, 1913.

changes that take place in the color and flavoring on keeping. Recently, another question has been raised, namely, if Quinine in solution with Acetic Acid is not partly changed to Quinotoxin. Consequently, it seems desirable to adopt in the revision a different formula.

The pharmaceutical journals have presented a number of proposed formulas and it has fallen to my lot to try many of these. Without going into a detailed account of the experiments or criticism of these formulas, I will submit the improved formula which I have recommended.

ELIXIR FERRI, QUININÆ ET STRYCHNINÆ PHOSPHATUM.

Soluble Ferric Phosphate	17.5	gm.
Potassium Citrate	5	gm.
Quinine	8.75	gm.
Strychnine	0.275	gm.
Phosphoric Acid	2	cc.
Alcohol	200	cc.
Glycerin	200	cc.
Compound Spirit of Orange	10	cc.
Purified Talc	30	gm.
Distilled Water, a sufficient quantity, To make	1000	cc.

Dissolve the Quinine and the Strychnine in the Alcohol and 100 cc. of Distilled Water to which has been added the Phosphoric Acid. Add to this the Compound Spirit of Orange. Dissolve the Soluble Ferric Phosphate and the Potassium Citrate in 100 cc. of warm Distilled Water. To this solution add the Glycerine and then the alkaloidal solution and sufficient Distilled Water to make the product measure 1000 cc. Mix the Purified Talc intimately with the liquid and then filter, returning the first portion of the filtrate until a transparent liquid is obtained. Lastly, wash the filter with a mixture of 1 volume of Alcohol and 4 volumes of Water until the filtered product measures 1000 cc.

In this formula the proportion of the medicinal ingredients is retained the same as in the present official formula, as it was not deemed desirable to make any change in the accepted strength or dosage. The use of glycerin as the sweetening ingredient in place of sugar has proven very satisfactory in elixirs containing iron salts and corrects the tendency of such elixirs to change color. The green tint of the product as at first prepared appears to

undergo no marked change after keeping for a year or more. Instead of using Aromatic Elixir as a diluent, the elixir is made in the process of the manipulation, the Compound Spirit of Orange being added, thus insuring the greatest amount of flavoring possible. The manipulation is an important factor in obtaining a satisfactory product and a reversal of the directions as to mixing will promptly demonstrate this.

DEODORIZED TINCTURE OF OPIUM.[1]

By Joseph W. England.

The official Deodorized Tincture of Opium is a solution of the water-soluble proximate principles of opium made from granulated opium and water, concentrated by evaporation on a water bath, washed with purified petroleum benzin and preserved with alcohol. The process eliminates resin, caoutchouc, ligneous matter, odorous principles, etc. The preparation is analogous to the old McMunn's Elixir of Opium.

The objection to the official method of making Deodorized Tincture of Opium is that it is tedious to carry out and the product, unless very carefully made, is apt to have a benzin-odor.

Various improvements in the official formula, including the paraffin-method, have been suggested, but the simplest and best procedure, in the judgment of the writer, is to make the preparation directly from deodorized opium, as advocated by the late Professor John M. Maisch (King's American Dispensatory, 1900, p. 1978). This has been done in the laboratory of Smith, Kline and French Co., for a number of years and with entire satisfaction.

The following method is recommended:

Deodorized Opium (containing 12 to 12.5 per cent. of crystallizable morphine) one hundred grammes	100 gms.
Alcohol, two hundred cubic centimeters	200 cc.
Water, a sufficient quantity to make one thousand cubic centimeters	1000 cc.

To one thousand cubic centimetres of *cool* water, in an evaporating dish, gradually add one hundred grammes of Deodorized Opium, mix and heat on a water bath for six hours; replacing

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[1] Presented at the annual meeting of the New Jersey Pharmaceutical Association, June 11, 1913.

water lost by evaporation. When cool, pour the mixture, as evenly as possible, upon a wetted, non-fluted paper filter in a funnel, returning the first portion of the percolate until it runs clear. Then percolate the residue on the filter with water until the percolate passes colorless and is only faintly bitter. Concentrate the percolates on a water bath, until they measure seven hundred cubic centimetres, cool, add two hundred cubic centimetres of alcohol, and filter through a paper filter.

Assay the final product by the process given under Tinctura Opii of the U. S. Pharmacopœia and adjust the volume of preparation, by the addition of water, so that each one hundred cubic centimetres shall yield not less than 1.2 nor more than 1.25 Gms. of crystallized morphine. By making the final volume nine hundred cubic centimetres, and assaying, the product can be most readily standardized.

In the making of Deodorized Tincture of Opium from deodorized opium, boiling water has been used, but, in the writer's opinion, the use of *cool* water, and then heating on a water bath, is preferable.

PHYLACOGENS:[1]

General Description.

Since 1910 the interest of medical circles has been excited by the extraordinary results reported as following the use of a new form of bacterial derivative in the treatment of acute and chronic infections, originated by Dr. A. F. Schafer, of Bakersfield, California, who first presented his discovery to the profession through the San Joaquin Medical Society, at Fresno, California, October, 1910, and later through the San Francisco Medical Society on January 14, 1911. Dr. Schafer's preliminary paper was published in the *Therapeutic Gazette,* April 15, 1911.

Theory: The Views of Dr. Schafer.

The principle upon which the use of these Phylacogens is founded is, briefly, the theory of multiple infections. The prin-

[1] In response to a request by the editor of this Journal for a brief article giving a summary of the nature, properties and uses of Phylacogens, Messrs. Parke, Davis and Company have sent a voluminous article of which this is an abstract.

ciple is supported by an extraordinary practical experience, supplemented by exhaustive and long-continued laboratory and clinical experimental work by Dr. Schafer.

Three facts are set forth by Dr. Schafer as the basis of this new therapy.

First: Practically all acute and many of the chronic diseases are caused by the metabolic products of pathogenic bacteria.

Second: The human subject is the host of micro-organisms that are pathologically latent but capable of setting up a disease process under certain conditions.

Third: The growth of infecting micro-organisms can be arrested and their effects neutralized by products derived from their development in artificial culture media.

Dr. Schafer is of the belief that all infections are "mixed infections," that except in rare instances there is no such thing as an infection by a single species of micro-organism; that while one species may predominate, the pathogenic process engendered by it is accelerated and intensified by the complicating presence of other organisms of other species: in other words, that in the course of an infectious disease the symptoms are due not only to the effects of a single species of organism (the specific infection), but to the influence of other organisms whose pathologic role is not insignificant, but which must be reckoned with in any successful scheme of therapeutics.

Dr. Schafer further believes that the human subject is at all times the host of a great variety of organisms and harbors these pathogenic bacteria without harm to itself during periods of physiological resistance, at or above par, and in the absence of any solution of tissue continuity. When the resistance is below par, or a solution of continuity of tissue occurs, the bacteria harbored by the human host assume pathological significance.

Furthermore, he contends that certain diseases, as typhoid fever, pneumonia, tuberculosis, erysipelas, rheumatism, and others, are objective and subjective symptomatic manifestations of the preponderance in the patient of the toxic and destructive products of the peculiar species of organisms to which the etiology of the disease is usually ascribed, as *B. Typhosus* in typhoid fever, *D. Pneumoniæ* in pneumonia, the *B. Tuberculosis* in tuberculosis, etc.; and, in addition, the symptoms are due in part at least to the destructive action of certain materials produced by complicating

organisms which are always present in great variety and number.

As an illustration, attention may be directed to the now commonly accepted idea that in pulmonary tuberculosis the greatest danger to the patient, much of the difficulty of the treatment, and many of the most notable symptoms, such as loss of weight, high temperature, disturbance of circulation, purulent expectoration, destruction of tissue, etc., are due to the complicating organisms, and if the so-called "mixed infection" can be checked or eliminated, efforts may be directed against the bacillus tuberculosis with far greater success than has heretofore been possible in the treatment of this condition.

Dr. Schafer points to the fact that the administration of bacterial vaccines to patients suffering from infection not infrequently fails of effect because the truth of the above assumption is not recognized, especially when the treatment consists in the use of a vaccine made from a single species of organism isolated from the patient. Bacterial vaccines made from a single species of organism proved successful in many cases, but the multiplicity of "combined" bacterial vaccines now in use points to the rapidly developing conclusion that the great majority of patients require something more than treatment with a vaccine made from one organism; the success attending the use of polyvalent bacterial vaccines made from a number of different species, even when used in pathologic conditions apparently due to one species, points to the likelihood of this theory being correct.

Name.

The term "Phylacogen" has been coined to distinguish the several new bacterial derivatives (devised by Dr. A. F. Schafer and produced by Parke Davis & Co.) from other remedial agents of similar character that may be offered to the medical profession. Each specific Phylacogen is further identified by the prefixion of the name of the pathological condition in which it is indicated—as Gonorrhea Phylacogen, Rheumatism Phylacogen, Pneumonia Phylacogen, etc.

The term "Phylacogen" (derived from two Greek words, phulax φύλαξ a guard, and gennan γενναω to produce) means "Phylaxin producer." Phylaxin is the name applied by Hankin to a defensive proteid found in animals that have acquired an artificial

immunity to a given infectious disease. Phylacogens are new process bacterial derivatives prepared by Parke, Davis & Company according to a method originated by Dr. A. F. Schafer and used in the treatment of infectious diseases.

Preparation of Phylacogens.

Phylacogens are neither "bacterial vaccines" nor "sera" as ordinarily understood. They are sterile aqueous solutions of metabolic substances or derivatives generated by bacteria grown in artificial media.

The Phylacogens are made from a lage number of species of the well known pathogenic bacteria, such as the several Staphylococci, Streptococcus pyogenes, Bacillus pyocyaneus, Diplococcus pneumoniæ, Bacillus typhosus, Bacillus coli communis, Streptococcus rheumaticus, Streptococcus erysipelatis, etc. The various organisms are present in the material before filtration in approximately equal proportions. The cultures are incubated at 37° C. for 72 hours or longer, the bacteria killed, after which a preservative consisting of 0.5 per cent. of phenol is added to the fluid, which is then filtered through porcelain. The basic Phylacogen, made in this manner, and used in the preparation of the several specific Phylacogens, is named "Mixed Infection Phylacogen." This basic Phylacogen is a "polyvalent" preparation, or Polyphylacogen, since the organisms are not from one strain only of a given species, but from cultures made at frequent intervals and from a variety of sources.

Each specific Phylacogen is prepared by modifying the basic material (Mixed Infection Phylacogen) by the addition of an equal amount of the filtrate obtained by growing and treating the organism considered to be predominant in the pathological condition to be treated; for instance, in the preparation of Rheumatism Phylacogen, the Streptoccoccus Rheumaticus is grown and treated similarly to the several organisms entering into the preparation of the basic Phylacogen. The filtrate obtained from the preparation of the rheumatism organism is added in equal amount to the Mixed Infection Phylacogen, and the resulting product given the specific name "Rheumatism Phylacogen." A like method is employed in the manufacture of the other specific Phylacogens, such as Pneumonia, Gonorrhea, Erysipelas Phylacogen, etc.

Culture and Safety Tests.

Aerobic and anaerobic culture tests are made of each lot of Phylacogen prepared, to determine whether the completed product is sterile. Coincidental safety tests of the same preparations are made by injecting relatively large doses subcutaneously into each of a series of animals; if the animals remain healthy the product is passed. A large number of the test animals are anesthetized, killed, and examined, ten days after injection; in each instance the autopsy discloses nothing more than a faint trace of tissue irritation at the site of injection.

Laboratory Experiments.

Careful investigations were conducted in the scientific laboratories for the purpose of determining the physiologic effects of the Phylacogens, and to demonstrate their safety when used therapeutically. These researches are still going on, now more than two years since the first investigations were begun.

Potency.

The degree of potency or energy of the Phylacogens has been carefully ascertained by means of experiments on laboratory animals (some eight hundred of which were used in these investigations). The Phylacogens were injected subcutaneously, intravenously, and intramuscularly, and were given internally. The results indicate that the average minimum lethal dose (by *intravenous* injection) per kilo of body weight of an animal is 11.90 c.c. By comparison, it would, therefore, appear that the average minimum lethal dose for a man of 150 pounds body weight is about 809.2 c.c. The suggested *subcutaneous* therapeutic dose is 2 c.c., to 20 c.c., for the average human (150 lbs. weight or 70 kilogrammes) or, 0.03 c.c., to 0.3 c.c., per kilo. The suggested *intravenous* therapeutic dose is ½ c.c. to 5 c.c., for the average human (see above) or, 0.00715 c.c. to 0.715 c.c. per kilo. The relatively (comparatively) nontoxic action of these Phylacogens, therefore, seems assured.

It would appear from correspondence that there is some confusion as to the potency of Phylacogens. The statement has been made several times that physicians are "afraid to use Phylacogens because they are dangerous" and Parke Davis & Co. have been re-

quested on several occasions to issue the statement that they are not dangerous. They cannot make any such a statement because, under certain circumstances, they *may* be dangerous. The proper statement is that relatively (comparatively) they are not dangerous. Sterile water or salt solution, improperly used, might be dangerous. There is not a drug in the entire Pharmacopœia that is not dangerous under some circumstances. Many of the more commonly used drugs are dangerous under certain conditions. Morphine, Strychnine, Chloroform, Ether, and so on through the entire list of powerful drugs—all are, in their proper place and given in the proper doses, and in the proper conditions, valuable therapeutic agents, but improperly used, under the wrong conditions, and in too large doses, they are certainly dangerous, and so with Phylacogen.

As a result of a great amount of experimental work on animals, it was found that the average least quantity of Phylacogen required to kill an animal, when injected intravenously with Phylacogen, was 11.9 per kilo of body weight of the animal, and that, by a simple problem in mathematics, it was shown that it would require about 800 c.c. to kill a man of 150 pounds in weight. It, therefore, is perfectly plain to be seen that, under some circumstances, Phylacogen is dangerous.

The literature suggests the administration of Phylacogen either subcutaneously or intravenously, and the range of dosage recommended is as follows:

Subcutaneous dose is 2 to 20 c.c., beginning with 2 c.c., and gradually increasing to 10 c.c.

Intravenous dose ranges from ¼ of a c.c., to 5 c.c.

What does this mean as regards the relative potency of Phylacogen? It means just this: That the least quantity of Phylacogen required to kill a human, weighing 150 pounds, on the average would theoretically be about 800 c.c. "On the average" indicates that in some instances it might take less and in some other instances it might require more to kill a 150 pound man. If Phylacogen was administered to a sick human it might require a good deal less under some conditions to kill the patient than it would in the case of a perfectly well person, but notwithstanding this fact, the largest dose suggested in the literature, for subcutaneous injections, is 20 c.c., or 1/40 of the average lethal dose for a 150 lb. human. Patients have received doses as large as 50 c.c., administered at one

time, and this dose repeated for several days, without any other result than to cure the patient of his disability. The largest dose suggested in the literature, for intravenous injection, is 5 c.c., or 1/160 of the average lethal dose for a 150 lb. human. A number of patients have received as high as 15 c.c., administered daily in the vein, with the result of curing the patient, but we do not recommend such doses. The highest dose suggested in the literature is ⅓ of this dose (5 c.c. as compared with 15 c.c.). "The relatively non-toxic action of these Phylacogens therefore seems assured."

Hematological Studies.

The results of elaborate studies in the research laboratories indicate that in most instances the blood of animals injected with the Phylacogens undergoes but slight change, the most notable being in the number of cellular elements. Practically all tests show, following the injection, a slight diminution in the number of red cells; and a fairly constant leukocytosis, but usually without alteration in the size or condition of the corpuscles. The hemoglobin content and the specific gravity are affected very little. A large number of blood-pressue tracings have been made, indicating that a depressor (blood-pressure-lowering) principle is present in the Phylacogen. The clotting time of the blood is slightly decreased.

Effects Upon the Heart.

The Phylacogen causes a distinct effect upon the heart and central nervous system, as evidenced by a rapid pulse, which may increase to fifty beats above the rate before injection, and an increase in temperature of one to five degrees.

Physiological Action.

The present use of the Phylacogen, prepared according to the method originated by Dr. A. F. Schafer, may be objected to by some practitioners on the ground of empiricism, and criticised because there is just now no proved scientific explanation of the exact mode of action of these Phylacogens.

The clinical results obtained thus far with these Phylacogens fully warrant their use even in the absence of a plausible theory explaining the method by which the curative action of Phylacogen is produced.

Anaphylaxis.

Extensive studies with laboratory animals were undertaken for the purpose of determining whether anaphylaxis, or dangerous sensitization of animals, could be produced by injections of these Phylacogens. No anaphylactic reactions (29) were observed in the experiments, which were most exhaustive.

Clinical Testing.

In order to obtain an abundance of clinical evidence to substantiate or refute the claims for the Phylacogens, a series of searching clinical tests was instituted in March, 1911, large quantities of the various Phylacogens were submitted to skilled clinicians, and these clinical tests are being continued at the present time. This investigation has furnished abundant evidence of the therapeutic value of the Phylacogens.

With an incredulity amounting to suspicion, and with every determination to be no man's dupe, a searching investigation was begun of Dr. Schafer's claims for his bacterial derivatives (Phylacogens). A vast mass of work has been done—in the laboratory, on animals, in the hospitals, at the bedside. Literally hundreds of reputable physicians have administered thousands of doses of the Phylacogens for rheumatism, gonorrhea, erysipelas, and mixed infections. A cool critical survey of the clinical results has convinced us that the Phylacogens possess great therapeutic power.

Reports have been received in detail of six thousand, three hundred and twenty-four (6324) cases of various conditions (from March 15, 1911, to May 30, 1913) treated with Phylacogens. These clinical reports include records from nine foreign countries as follows: Canada, England, Scotland, Mexico, Cuba, South Africa, New South Wales, New Zealand, Jamaica, W. I. These together with the United States, make ten countries where Phylacogens have already been tested clinically. This series includes cases of all kinds without regard to age, sex, nationality, color, condition, environment, part of the United States, Physician in attendance, whether hospital or private case, whether suited or unsuited for treatment. Of this series of 6324 cases, 5270 are reported as cured, and one thousand and fifty-four (1054) are arbitrarily recorded as failures.

THE TOTAL STATISTICS.

Total cases	6324	
Recovered	5270	(83 per cent.)
Failed	1054	(17 per cent.)

These figures need some explanation. To obviate any criticism of padding records or changing findings, or being over-enthusiastic or exaggerating, the statement of the physician reporting the case has been made the arbitrary dividing line. If he stated that his case recovered, we put it down as "recovered"—if he stated that it failed, no matter what the reason was, it was entered as a failure. The 1054 failures, therefore, include patients who were moribund, their death was inevitable. It includes cases that were not completely treated, the records showing very plainly that for one or another reason the Phylacogen treatment was given up before enough had been administered to do any good. In some instances the patient or the physician became frightened at the reaction and refused to continue, or the physician did not think that the Phylacogen would do any good and refused to go on, or the patient did not think he was getting well fast enough and refused to permit further injections. It also includes cases of wrong diagnosis, where subsequent investigation disclosed the error in diagnosis, so that Phylacogen was given under a misunderstanding and it could not have done any good. The classification of the clinical reports is extremely conservative and if unfairness be charged it has been unfairness to the Phylacogen. In other words, the showing above is the worst possible showing, and, under the circumstances, it is a splendid record.

REACTIONS.

Experience has shown that the injection of Phylacogen is usually followed by local or systemic reaction, or both. These may vary from very slight to quite pronounced reaction.

PHYLACOGEN BIBLIOGRAPHY.

1. A Modified Vaccine Therapy Based upon the Theory of Multiple Infection and Quantitative Reaction. By Dr. A. F. Schafer, Bakersfield, Cal. *Therapeutic Gazette,* April 15, 1911.
2. Phylacogen. By Dr. L. Daily, Houston, Tex. *Medical Bulletin of Harris Co. Med. Soc.,* Houston, Tex., March, 1912, p. 21.

3. Results Obtained with a Modified Vaccine. By Dr. Louis D. Green, San Francisco, Cal. *Cal. State Jour. of Med.*, April, 1912, p. 160.
4. Gonorrhea Phylacogen. By Dr. G. K. Swinburne, New York. *N. Y. Med. Record,* May 25, 1912, p. 975.
5. Schafer Vaccine Treatment for Rheumatism. By Dr. G. C. Crandall, St. Louis, Mo. *Jour. of the Mo. State Med. Asso.*, June, 1912, p. 492.
6. Treatment of Rheumatism with Rheumatism Phylacogen. By Dr. Edw. B. Richey, Louisville, Ky. *Charlotte Med. Jour.*, July, 1912, p. 12.
7. Rheumatism Phylacogen. By Dr. W. H. Foreman, Indianapolis, Ind. *Indianapolis Med. Jour.*, July, 1912, p. 293.
8. New Treatment for Rheumatism. Editorial in the *Arkansas Med. Jour.*, July, 1912, p. 55.
9. Experience with Phylacogens in Certain Bacterial Diseases. By Dr. W. A. Jenkins, Louisville, Ky. *Medical World,* July, 1912, p. 285.
10. Rheumatism Phylacogen. By Dr. J. T. Dunn, Louisville, Ky. *American Practitioner,* Aug., 1912, p. 364.
11. Rheumatism Phylacogen. By Dr. Geo. Wood, Indianapolis, Ind. *Medical Progress,* Aug., 1912.
12. Acute Articular Rheumatism Treated with Phylacogen. By Dr. Edw. B. Richey, Louisville, Ky. *Kentucky Med. Jour.*, Aug. 15, 1912, p. 647.
13. Gonorrheal Rheumatism. By Dr. J. A. O. Brennan, Louisville, Ky. *Kentucky Med. Jour.*, Aug. 15, 1912, p. 646.
14. What Nurses Should Know About Treatment with Sera, Vaccine, Toxins, and Phylacogens. By Miss Emma Nixon, member Cal. State Nurses' Asso. *Pacific Coast Jour. of Nursing,* Sept., 1912, p. 416.
15. Phylacogens. *Pacific Pharmacist,* Aug., 1912, pp. 85–86.
16. Secondary Infections in Pulmonary Tuberculosis. By Dr. I. H. Alexander, Pittsburgh, Pa. *New York Med. Jour.*, Oct. 5, 1912, p. 677.
17. The Treatment of Gonorrheal Rheumatism. By Dr. C. J. Broeman, Cincinnati, O. *Lancet-Clinic,* Oct. 12, 1912, p. 386.
18. General Surgical Infections—A Preliminary Report of the Use of Mixed Infection Vaccine (Schafer). By Dr. Chas. A. Hill, Pittsburgh, Pa. *New York Med. Jour.*, Oct. 19, 1912, p. 793.
19. The Use of Mixed Infection Vaccine in Skin Infections. By Dr. J. G. Burke, Pittsburgh, Pa. *New York Med. Jour.*, Nov. 2, 1912, p. 895.
20. Articular Rheumatism, Treated with Phylacogen. By Dr. J. A. Guthrie, Huntington, W. Va. *Therapeutic Notes,* Sept., 1912, p. 100.
21. Recurring Articular Rheumatism and its Treatment with Phylacogen. By Dr. F. C. Walsh, Mukwonago, Wis. *Therapeutic Notes,* Sept., 1912, p. 95.
22. The Use of Gonorrheal Phylacogen in the Treatment of Gonorrheal Rheumatism. By Dr. H. L. Kretschmer, Chicago, Ill. *Therapeutic Gazette,* Jan. 15, 1913, p. 15.
23. Phylacogens, Therapeutics, Materia Medica and Pharmacy (text-books). By Dr. S. O. L. Potter, San Francisco, Cal. Published by P. Blakiston's Son and Co., 1912.
24. Treatment of Rheumatism. By Dr. A. W. Moore, Portland, Oregon. *Northwest Medicine,* Nov., 1912, p. 332.

25. Treatment of Rheumatism with Phylacogen. By Dr. F. P. Dorsey, Hartington, Nebr. *Western Medical Review,* Nov., 1912, p. 606.
26. Rheumatic Affections of some of the Special Organs. By Dr. J. J. Kyle, Indianapolis, Ind. *Therapeutic Gazette,* Nov. 15, 1912, p. 770.
27. A Case of Chorea Cured with Rheumatism Phylacogen. By Dr. T. R. Rice, Petersburg, Ind. *Therapeutic Notes,* Nov., 1912, p. 114.
28. A Case of Articular Rheumatism Treated with Phylacogen. By Dr. F. L. Smith, Lucas, Kans. *Therapeutic Notes,* Nov., 1912, p. 122.
29. Phylacogens. By F. I. Lackenbach, San Francisco, Cal. *Cal. State Jour. of Med.,* Dec., 1912, p. 514.
30. Treatment of Gonorrheal Rheumatism. By Dr. V. D. Lespinasse, Chicago. *Medical Standard,* Dec., 1912, p. 433.
31. Phylacogen in a Case of Rheumatism and Asthma. By Dr. F. H. Giles, Braintree, Mass. *Medical World,* Dec., 1912, p. 533.
32. Cases Treated with Rheumatism Phylacogen. By Dr. F. J. Fralick, Greenville, Mich. *Medical Summary,* Dec., 1912, p. 317.
33. Gonorrheal Arthritis. By Dr. Geo. A. Holliday, Pittsburgh, Pa. *New York Med. Jour.,* Dec. 7, 1912, p. 1168.
34. Mixed Infection Vaccine in the Treatment of Myalgia and Arthritis. By Dr. R. E. Brenneman, Pittsburgh, Pa. *New York Med. Jour.,* Nov. 23, 1912, p. 1067.
35. Rheumatism Phylacogen. By E. J. Fleetwood, M.D., Wakefield, Neb. *Western Medical Review,* Jan., 1913, p. 31.
36. Report of a case of Chronic Gonorrhea treated with Phylacogen. By W. E. Stewart, M.D., Norman, Okla. *Jr. Okla. State Med. Asso.,* Dec., 1912, p. 323.
37. The Use of Rheumatism Phylacogen in Chronic Rheumatism. By E. B. Richey, M.D., Louisville, Ky. *Kentucky Med. Jour.,* Nov. 15, 1912, p. 853.
38. The Treatment of Erysipelas with Phylacogens. By W. A. Jenkins, M.D., Louisville, Ky. *Kentucky Med. Jour.,* Nov. 15, 1912, p. 855.
39. Mixed Infection Phylacogen. By E. S. Allen, M.D., Louisville, Ky. *Kentucky Med. Jour.,* Nov. 15, 1912, p. 855.
40. Phylacogen in Acute Articular Rheumatism. By J. S. Lowry, M.D., Smyrna, Tenn. *Medical World,* May, 1913, p. 206.
41. Clinical Report of Cases treated with Phylacogens. By F. C. Smith, M.D., Keokuk, Iowa. *Buffalo Med. Jour.,* Feb., 1913, p. 392.
42. Experience with Phylacogen. By E. L. Henderson, M.D., Louisville, Ky. *Louisville Monthly Jour. of Med. and Surg.,* Feb., 1913, p. 257.
43. Observations with Phylacogens in General Practice. By K. F. Snyder, M.D., Freeport, Ill. *Medical Herald,* April, 1913, p. 151.
44. Phylacogens. (Text-book "Practice of Urology.") By C. H. Chetwood, M.D., LL.D., New York, 1913, pp. 82 to 90.
45. Phylacogens: Unique Therapeutic Results. By B. F. Zimmerman, M.D., Louisville, Ky. *Lancet-Clinic,* Feb. 15, 1913, p. 184.
46. Phylacogens as a Cure for Rheumatism, Mixed Infections and Gonorrhea. By Gustav Schirmer, M.D., Chicago, Ill. *Medical Fortnightly,* Mar. 10, 1913, p. 89.

47. Discussion on Phylacogens. By J. W. Hassler, M.D., New York. *Journal Am. Inst. of Homeopathy,* Mar., 1913, p. 923.
48. Treatment of Erysipelas in Infants by means of .Vaccines. By E. M. Sill, M.D., New York. *Medical Record,* May 29, 1913, p. 573.
49. Gonorrheal Opthalmia Treated with Gonococcus Vaccines. By W. K. Mittendorf, M.D., New York. *Medical Record,* Mar. 8, 1913, p. 428.
50. An Experimental Therapy in Hay Fever. By S. F. Hogsett, M. D., Pittsburgh, Pa. *American Medicine,* April, 1913, p. 254.
51. The Treatment of Infections. By E. H. Troy, M.D., McAlester, Okla. *International Jour. of Surgery,* Apr., 1913, p. 129.
52. Aiding the Protective Processes of the Body. Editorial. *Therapeutic Gazette,* Mar. 15, 1913, p. 169.
53. Clinical Experience with Phylacogens. By S. Pirosh, M.D., Baltimore, Md. *Charlotte Medical Jour.,* Mar., 1913, p. 153.
54. Report of Case of Acute Art. Rheumatism responding to Rheumatism Phylacogen. By John H. Nowlin, M.D., Chicago, Ill. Pub. *Therapeutic Notes,* March, 1913, p. 59.
55. A Case of Septic Endocarditis treated with Mixed Inf. Phylacogen. By Peter C. Clemensen, M.D., Chicago, Ill. Pub. *Therapeutic Notes,* March, 1913, p. 60.
56. Vaccines and Phylacogens in Gonorrheal Rheumatism. By W. L. Champion, M.D., Atlanta, Ga. *Therapeutic Notes,* March, 1913, p. 61.
57. The Treatment of Typhoid Fever with the Phylacogen or Serum Vaccine of Schafer. By E. P. Benoit, M.D., Montreal, Canada. Published "L'Union Medicale du Canada," May, 1913, p. 249.
58. Treatment of Various Infections with the Bacterial Filtrate of Schafer. Editorial. *Revista Medica Cubana,* April, 1913, p. 187.
59. Acute Articular Rheumatism. By Dr. Victorino Cabrera, Havana, Cuba. *Revista Medica Cubana,* April, 1913, p. 188.
60. Acute Articular Rheumatism. By Dr. Eurigne Nunez and Claudis Basterrecher, Havana. *Revista Medica Cubana,* April, 1913, p. 189.
61. Chronic Articular Rheumatism. By Dr. Tomas V. Coronado, Havana. *Revista Medica Cubana,* April, 1913, p. 190.
62. Polyarticular Inflammatory Rheumatism. By Dr. C. E. Kohly, Havana. *Revista Medica Cubana,* April, 1913, p. 191.
63. Chronic Articular Rheumatism. By Dr. Francisco H. Alvarez, Havana. *Revista Medica Cubana,* April, 1913, p. 192.
64. Acute Rheumatic Arthritis. By Dr. F. Alvarez, Havana. *Revista Medica Cubana,* April, 1913, p. 193.
65. Pyosalpinx. By Dr. Ignacio Plasencia, Havana. *Revista Medica Cubana,* April, 1913, p. 195.
66. Septicemia from Incomplete Abortion. By Dr. Rafael Nogueira, Havana. *Revista Medica Cubana,* April, 1913, p. 196.
67. Puerperal Septicemia. By Fernandez Silva, Havana. *Revista Medica Cubana,* April, 1913, p. 196.
68. External Otitis Circumscribing Both Ears. By Dr. Vicente Gomez, Havana. *Revista Medica Cubana,* April, 1913, p. 197.

69. Chronic Asthmatic Bronchitis. By Dr. Antonio Cueto, Havana. *Revista Medica Cubana,* April, 1913, p. 198.
70. Bronchial Asthma. By Dr. Antonio D. Albertine, Havana. *Revista Medica Cubana,* April, 1913, p. 200.
71. Bronchial Asthma. By Dr. Ignacio Benito Plasencia, Havana. *Revista Medica Cubana,* April, 1913, p. 201.
72. Chronic Gonorrhea and Orchiepididymitis. By Dr. Antonio Cueto, Havana. *Revista Medica Cubana,* April, 1913, p. 203.
73. Gonorrheal Rheumatism. By Dr. Francisco deP. de Solis, Havana. *Revista Medica Cubana,* April, 1913, p. 203.
74. Gonorrheal Rheumatism of the right hand. By Dr. Luis Barbero, Havana. *Revista Medica Cubana,* April, 1913, p. 205.
75. Gonorrheal Conjunctivitis and Iritis. By Dr. Carlos E. Finlay, Havana. *Revista Medica Cubana,* April, 1913, p. 206.
76. Acute Gonorrheal Arthritis of the left knee. By C. E. Kohly, Havana. *Revista Medica Cubana,* April, 1913, p. 207.
77. Vaccine in Post-operative Pneumonia. By E. S. Allen, M.D., Louisville. *Kentucky Med. Jour.,* May 15, 1913, p. 422.

THE NECESSITY OF ESTABLISHING AN INTERNATIONAL PHARMACOPŒIAL BUREAU.[1]

By A. Tschirch.

Of the many ideas advanced by the thinking and original Ostwald, the expression that in intellectual life energy must be conserved is one of the most productive of thought. We should not only be saving of coal and water, but likewise economical of intellectual power. The same work should not be performed at ten different places, when with the same or less expenditure of energy it can be accomplished at some central point.

This thought of Ostwald's is applicable to many spheres of endeavor, but to none so much as pharmacopœial revision. In all civilized lands we see pharmacopœial committees at work, all trying to attain as much as possible a complete and perfect review of the literature pertaining to pharmacy and materia medica. In every land the whole literature is scanned to make the revision more useful and complete—and in every land the work is done independently of other bodies. And the fact is conspicuously brought out that in the German publications, the English and American journals, and in the French, one only gets a report or an abstract of an article,

[1] Translated by John K. Thum, Ph.G.

or an abstract of a report of an article. So each country becomes acquainted only with the works which appear in one's own language through more or less reliable reports. Through this much valuable work is lost. It often happens that the same work is abstracted two or three times, an error is repeatedly mentioned and must be refuted two or three times. In this manner much energy is unprofitably consumed.

The practical Americans have long been aware of this part of pharmacopœial revision and have taken means to overcome it. For some time the Treasury Department Public Health and Marine Hospital Service of the United States publishes yearly under the title Digest of Comments on the Pharmacopœia of the United States of America, Washington, Government Printing House, a short report of pharmacopœial articles appearing for the year. The references to the articles are complete so far as the title is concerned. But the text is too short for one to obtain all that is necessary. This institution should be enlarged upon. But this can only be brought about by centralizing the work. This, to my mind, *is the first problem of establishing an International Pharmacopœial Bureau.* If the different civilized countries create such a pharmacopœial bureau the library should be combined of all the pharmaceutical publications of the earth, and in this bureau regular and detailed abstracts of all pharmacopœial articles should be made; in this manner a central office could do the same work and accomplish it in a more reliable manner than a dozen different offices whose reporting is never exhaustive and performed in a trustworthy manner. These abstracts should be published simultaneously in German, French, and English, and given out in yearly volumes. Of course, this would necessitate the establishment of a Bureau provided with two or three linguists of sufficient experience to draw from the pharmacopœial publications of the main countries in a uniform and rapid manner so that the reports could appear a short time after the close of the year. The reports should exclude all scientific matters which do not have a direct bearing upon pharmacopœial revision. On the contrary, all work relating to drugs, the establishment of their identity, methods of assay, and all other data of like import should be worthy of notice.

These references should be bound in volumes of 1000 pages each.

But the abstracting activity should not be the only mission of this International Pharmacopœial Bureau. A wider field should be

a laboratory where careful attention could be given to the various methods of drug assay, both qualitative and quantitative, and comparisons made between methods now official and proposed. So only will we be successful in finding the best and simplest methods and bring them international recognition. And, as I mentioned at the Brussels Conference in 1902, it is not sufficient to give the alkaloidal content of a drug; it is also necessary to state in which manner it is best determined. For it is well known that the methods in the several pharmacopœias lead to very different results. Hence, there should be connected with this International Pharmacopœial Bureau a laboratory which should have, under the guidance of the directors of the Bureau, the services of an active, well-trained apothecary.

As the seat of this Bureau I would suggest the city of Bern, where so many international bureaus are successfully established, and I would also suggest that it would be well for this International Bureau to be connected with the Schweizeriche Sanitary Board—temporarily, at least—until it is strong enough to stand on its own feet.

To bring about the realization of this plan it would, to my mind, only be necessary for the Schweizeriche Apothekerverein, through the Swiss Sanitary Board's highest Council, to make the proposal and invite a conference of pharmacopœial experts from all interested countries to consider the plan and eventually form some program for action.

BERN, 1913.

CONCERNING INSTRUCTION IN PHARMACY AND THE CONFERRING OF DEGREES.[1]

BY B. E. PRITCHARD.

The Druggists' Circular in its issue for May, 1913, contains an editorial upon "Some Common Misconceptions," and the editor tells his readers that "there seems to be a great deal of misunderstanding" about a large number of things connected with pharmacy, as well as several other matters, and reaches the very sane

[1] Read at the annual meeting of the Pennsylvania Pharmaceutical Association, June, 1913.

conclusion that if we "get a good view of any situation as it actually exists we shall not be misled by expressions of unbaked ideas by others."

In the course of this editorial I have found one paragraph that serves my purpose as a text in the writing of this paper, which follows:

"Regarding the colleges of pharmacy and what they teach and do not teach, we are glad to be able to say that we believe the usual course given in *The Average College of Pharmacy,* backed up by the three or four years of practical experience required by most of the boards of pharmacy, fits a man or woman of ordinary intelligence and education for the work usually required of a pharmacist."

This statement leads up to the query what constitutes an "average college of pharmacy"?

The same journal in its issue for April, 1913, contains another editorial in which reference is made at some length concerning the action taken by the New York Education Department in its annual revision of colleges of pharmacy to be recognized in that state, in the course of which the statement appears "The last time the list was revised the names of three or four schools were dropped, among them being that of the oldest, perhaps the largest, and by many considered the best college of pharmacy in the country." Now while the fact as stated remains, the recognized list carries the names of many obscure schools of pharmacy located in various states extending all the way from Maine to Nebraska. So that to find an average college of pharmacy one is called upon to go far afield in the search. The right to graduate from a college of pharmacy is contingent upon the percentage of good marks made by the student in the opinion of the examiners of the particular school from which graduation is sought. The right to become registered in any state as a pharmacist is based upon the percentage made in the tests submitted by the respective boards of pharmacy. Now those who constitute the examiners in colleges of pharmacy and those who serve on boards of pharmacy are men of like calibre and similar attainments, approximately, at least, hence the same wide differences of opinion as to the fitness of students for graduation may exist as we find mentioned in a very excellent editorial appearing in the *Bulletin of Pharmacy* in its issue for April, 1913, from which we make this quotation:

"Some years since, for instance, when a practical test was made at one of the meetings of the National Association of Boards (of pharmacy) it was found that the members in attendance graded the same set of replies anywhere from 60 to 82 per cent."

Now when it is remembered that the students whose papers were being passed upon were, presumably, at least, all graduates of "reputable, recognized colleges of pharmacy," is it to be wondered at that one questions why should these things be?

When great minds differ so widely, how is the humble would-be student going to arrive at a safe conclusion in selecting a school in which to prepare himself for his life work?

If one would like to form some definite idea as to how far removed from the ideal are the colleges of pharmacy of to-day, and how widely divergent are the views of the men who are engaged in conducting these schools, let him take up the volume of the proceedings of the thirteenth annual meeting of the American Conference of Pharmaceutical Faculties, an organization which carries in affiliation 35 schools engaged in the teaching of pharmacy.

It is a book containing 92 pages of printed matter, each page 6 by 9 inches. I have read this book and was greatly interested in the questions discussed and the remarks of those who did the discussing, but when adjournment was reached, so far as I was able to arrive at a conclusion of the whole matter, there remained 35 different opinions as to just what constitutes a good average college of pharmacy.

The capacity for learning as it exists among human beings has a wide range. One person, as is frequently noted, can absorb as great a fund of information in one-half, or even less, time than another person under the same teaching. A mere hint ofttimes results in leading a thoughtful person into wider range of knowledge of a particular study than would ten years of skillful teaching upon the part of trained instructors impart to another person, less fitted by nature to assimilate knowledge.

For these reasons, then, the query "Should the minimum pharmacy course extend over three years?" is not capable of receiving a definite reply. The course necessary in pharmacy is extremely flexible in application and cannot be arbitrarily fixed.

John Brown, for instance, with a retentive memory and capable of giving close attention to his studies, with an open mind to the lectures during class hours, might be able to obtain such knowledge

of pharmacy as to fit him for passing a creditable examination in one year. On the other hand, John Smith, slow to assimilate, incapable of close application, not fitted by nature or disposition to listen attentively and absorb during lecture periods, might find it necessary to spend three years in a college of pharmacy before he could measure up to the required percentage that would graduate him. To my own way of thinking, there can be no such thing as a fixed minimum course in pharmacy, or any other study, for that matter. Each individual student should be permitted to graduate when he or she has shown ability to creditably meet the tests laid down. You may be able to reach that point in one year, while I might find it necessary to spend two or three or four years before being able to measure up. Length of time, therefore, can have no place in the matter of reaching the goal, and to make an arbitrary rule that any certain number of years shall constitute a minimum course in pharmacy is wrong in practice, however valuable it may be in theory.

One of the most serious, and deservedly so, criticisms attaching to labor unions is that they hold the best men in their membership back by making the standard of accomplishment to fit the capacity of the weakest brother, and are not colleges of pharmacy doing the same thing in the fixing of a minimum course in the study of pharmacy? Penalizing the bright students by compelling them to serve time because of the inability of the duller ones to meet the pace.

In the fixing of an average there must of necessity be recognized highest and lowest points. Now when so august a body as the Education Department of a great state says to the graduates of what has been herein before stated to be "by many considered the best college of pharmacy in the country," "The Board of Pharmacy will not even admit you to its examinations;" while at the same time students from some small, obscure, practically unknown school, located somewhere in North Dakota are given the glad hand of full recognition by the same aforementioned august body of educators, what is there left for me to do other than to return to my starting point and again propound the query, "What constitutes an average college of pharmacy?"

Now, having satisfactorily failed to reach a conclusion as to whether the minimum pharmacy course should extend over three years, I find myself face to face with that other perplexing problem, "What degrees should be conferred on the completion of two

or three or four years in a College of Pharmacy?" And in this instance I trust I shall not be so successful in showing "how not to do it."

In taking up for consideration this subject I am fortunately not handicapped by the possession of any rear end initials myself. The only letters attaching to my cognomen are those which precede my family name, and I have troubles enough in keeping them on straight with my correspondents. I must confess that the agitation concerning the matter of degrees that seems to have stirred to the depths some men's feelings has never touched me. Hence like the qualifications sought for in the selecting of a jury, my profound ignorance of the subject may stand me well in hand. It has always seemed to me that the having of a quarter section or so of the alphabet tacked on to the hind end of one's signature does not add one jot nor tittle to either the knowledge or usefulness of the bearer thereof. The satisfaction of knowing well one's profession and being able to solve its complex problems as they arise is where all the glory lies—and it does not make it any easier to accomplish this achievement to know that it would tax the capacity of a more than ordinary sized card to carry all the symbols of the various degrees that men have seen fit to confer upon one. It gave me profound satisfaction to read not long since that the Honorable Wm. E. Gladstone held similar views upon this subject, and persistently refused to accept any degree that schools of learning and other institutions were anxious to confer upon him. It is comforting to one's sense of satisfaction to know that his is not the only wise head. I have not, however, been compelled to dodge any titles that were aimed in my direction, and in that respect I hold an advantage over Premier Gladstone.

Of late years I have noticed signs conspicuously displayed over the entrances to plumbing establishments bearing the inscription "Registered Plumber," so that the attaching of the symbols R. P. to one's name leaves it an open question as to whether one is a registered pharmacist or a registered plumber.

In the issue of the *Journal of The American Pharmaceutical Association* for April, 1913, Otto A. Wall, Ph.G., M.D., covers eight pages in the setting forth of his views concerning degrees in pharmacy, in the course of which he submits 48 different symbols attaching themselves to pharmaceutical degrees, many of them, of course, being different abbreviations in common use to indicate the

same degree. Touching the contention of our own Professor Remington that P. D. as an abbreviation legitimately applies only to the degree Doctor of Pharmacy, and that its use as indicating any other degree is clearly a species of larceny, so to speak, Dr. Wall tells his readers that "No institution can claim exclusive right to an ambiguous initial abbreviation for any particular study . . . and if there are any who feel aggrieved at the resulting ambiguity they can use correct academic syllabic abbreviations for their own degrees."

Authorities contend that in the beginning there was but one degree conferred in pharmacy, that of Ph.G. meaning that the bearer of the same had been graduated by a college of pharmacy, or indicating merely the fact that the owner had completed a certain prescribed course in pharmacy of which his diploma bore evidence and the symbol Ph.G. was the sign thereof. Hence rightly construed the title Pharmacy Graduate, or its symbol Ph.G., is not in any sense to be considered as a degree. So far as I have been able to consult authority on the subject of degrees in pharmacy there are but three that carry the right to attach to one's name with any real meaning, these are Bachelor, Doctor, Master. Bachelor of Pharmacy means, just as the term bachelor does when applied to an unmarried man—an incomplete man—so Bachelor of Pharmacy means an incomplete pharmacist. Thus it would seem that when a student has graduated from a limited prescribed course of study in pharmacy he should be granted the degree of Bachelor of Pharmacy, Ph.B. instead of as is now the practice the term Graduate in Pharmacy, or Ph.G. When a student has attained to the possession of this inferior degree, and has succeeded by right thereof in becoming registered as a pharmacist on the roll of the State Board of Pharmacy he should earnestly strive at as early a stage in his career as possible to arrive at the top by fitting himself through study and experience and the taking of a post-graduate course to earn that highest degree in his profession that can be reached in course, Doctor of Pharmacy.

The degree Master of Pharmacy should never be conferred upon any one who has merely spent a few terms in a College of Pharmacy, but should by all means be sacredly reserved and held inviolate for conferring upon such good men and true as have by signal service rendered, unselfishly, and for the good of their fellows, earned the right of recognition and to have that honorable title

conferred as a mark of appreciation by a University of the highest rank. Not through self seeking but for reason that the institution honors itself in soliciting the privilege of bestowing this degree upon one who has proven himself worthy to wear it.

CURRENT LITERATURE.

PRECIPITATING ALKALOIDS BY LLOYD'S REAGENT.

In a preliminary note published in the *Journal of the American Chemical Society* for June, 1913, p. 837, Sigmund Waldbott calls attention to John Uri Lloyd's patent involving reactions of intense scientific interest and wide scope, the extent of which has been perceived by no one more clearly than the discoverer himself. Reserving a more detailed statement of his labors for future publication, Professor Lloyd, at the beginning, has kindly given Mr. Waldbott the privilege of investigating the chemical and physical nature of his reagent.

This reagent is essentially hydrous aluminium silicate, derived from Fuller's earth. The reagent has the startling quality of precipitating alkaloids completely from neutral or acid solutions thereof. The alkaloid may be recovered by treatment with a base and an alkaloidal solvent. Quinine bisulphate was used exclusively in the following experiments, since Professor Lloyd himself has extended his research over a great number of alkaloids and alkaloidal salts, including those occurring in plants.

The reagent had approximately the following composition: H_2O, 17. 41 per cent.; SiO_2, 55.30 per cent.; Al_2O_3, 9.82 per cent.; Fe_2O_3, 14.18 per cent.; CaO, 1.58 per cent.; CO_2, per cent. not determined. Heating the material to about 130° did not destroy its peculiar activity; but a red heat expelled an additional quantity of water rendering the reagent inert. When the reagent is exhausted with hydrochloric acid, the residual earth is still effective. The activity of the reagent is not impaired by concentrated nitric acid or by *aqua regia*. After the alkaloid has been removed from its combination with the reagent, the residual material retains the full effect. This process results in a jelly difficult to filter and slow to settle it; it is precipitated readily by addition of an acid, or an alkaloidal salt. In drying, the jelly shrinks to a very small bulk;

conversely, the solid expands remarkably in contact with water. The jelly precipitates inorganic salts also, *e.g.*, barium chloride, lead acetate, zinc sulphate, etc.

It will be observed that the phenomenon is one of colloidal chemistry. The thought suggested itself that water-deposited clay might show the same action; indeed, it was found by Mr. Waldbott last summer that the fine blue clay so abundant in the hills of Cincinnati, after treatment with hydrochloric acid, had the same effect upon alkaloidal salts, rather faintly as may be expected, yet very distinctly.

In the course of this investigation, other colloidal materials were also examined, and it was found among others that colloidal silicic acid, or colloidal arsenious sulphide plainly precipitated quinine sulphate.

POISONING BY GINKGO.

Several botanists after dissecting the fruits of *Ginkgo* have developed what appeared to be ivy poisoning. As the juice of the *Ginkgo* produced an immediate irritation of the skin, it was suspected that the rash which developed the following day was due to this. Later tests proved this to be the case. The poison is in the outer fleshy layer. It does not affect all people, since the gardeners at Smith College and at Mount Holyoke College have never been poisoned by handling the *Ginkgo* fruits, but a gardener in Elyria, Ohio, who cares for a fruiting tree in the yard of Mr. William G. Sharp, writes that he is poisoned every fall by handling the fruits. The irritation produced is greater than that of poison ivy, and the infection spreads more persistently and is communicated from one person to another. Pustules rarely form, however, as in ivy poisoning, but there is a heavy red rash, attended by the formation of welts in severe cases.—ANNA M. STARR, Mount Holyoke College, South Hadley, Mass., in *The Botanical Gazette*, March, 1913, p. 251.

DRUG DETERIORATION.

The Wayne County (Michigan) Medical Society recently appointed a committee to coöperate with a similar committee appointed by the Detroit Retail Druggists Association to investigate the question of deterioration of drugs. Dr. W. J. Wilson, Jr., of Detroit, calls attention to this fact and sends a copy of the report:

The Committee on Drug Deterioration appointed by the joint meeting of the Detroit Retail Druggists Association and Wayne County Medical Society would respectfully report:

Recent investigations of the fluidextracts show that with few exceptions they retain their potency for a number of years when kept under proper conditions; that is, without access to air, or exposure to light.

With such drugs as hydrogen peroxid in which the absolute limit of potency is eighteen months, and the probable limit from six to twelve months, we would recommend that the manufacturers state on the label the date of manufacture as well as the limit of potency.

We would recommend that the practice of keeping all liquid preparations, such as tinctures and fluidextracts which deteriorate on exposure to light, preferably in light-proof cupboards, or in amber-colored bottles not exposed to direct sunlight, with the usual precautions of a tight-fitting and air-proof stopper, be made universal.

We would also recommend that the subject of drug deterioration be made one of the leading topics for discussion in all the state and national pharmaceutical and medical societies in the meetings of the near future.—*Jour. A. M. A.*, June 7, 1913, p. 1810.

BLAMING THE DRUGGIST.

When some years ago the Council on Pharmacy and Chemistry investigated Lactopeptine it was claimed that "Lactopeptine contains the five active agents of digestion—pepsin, diastase (veg. ptyalin), pancreatin, lactic acid and hydrochloric acid—combined in the proper proportion to insure the best results." The Council's examination indicated that Lactopeptine contained more than 90 per cent. of milk sugar. The amount of pepsin was somewhat less than 10 per cent. of official pepsin. The amount of lactic acid was found to be 3 per cent. Neither diastase nor pancreatin could be found and hydrochloric acid was present in mere traces only. Examination of another specimen not only failed to show the presence of diastase and pancreatin but also failed to show any appreciable amount of pepsin.

What have the promoters of Lactopeptine done to offset this report? The November, 1912, "Doctor's Factotum," an advertising sheet, contains the following:

"The mere presence of digestive enzymes like pepsin, trypsin, amylopsin, etc., is *not* sufficient.

"Stimulation, inhibition and activation are intimately bound up in the cycle of digestion and are responsible for its proper development and course."

After suggesting that after all it does not matter much whether enzymes are present or not we read further:

"And the most vital and most important fact in regard to Lactopeptine is that it is a *combination,* acts as a combination and secures results only to be gotten from such a combination."

Then, of course, it is suggested that only the Lactopeptine people can make this combination. Finally to cap the climax the suggestion is made that if the medicine does not do what is expected of it the druggist has practiced substitution. Thus the last word in the above-named advertising sheet is:

"Failure to get results usually means *substitution.*

"Therefore, write it thus: Lactopeptine (Genuine) and send your patient to an honest pharmacist."

We extend our sympathy to the poor druggist who so often is made the "goat" by proprietary medicine concerns. Let us hope, however, that this reflection on the druggist will not only be the cause of further discrediting Lactopeptine but also the equally discreditable substitute, Pulvis Pepsini Compositus, which the druggists have officialized in their National Formulary—this despite the fact that in 1907 the then president of the American Pharmaceutical Association (the late Mr. Leo Eliel of South Bend, Ind.) called the attention of the medical profession (*Jour. A. M. A.*, April 6, 1907, p. 1198) to the fact that the pharmacists had since 1876 been aware of the worthlessness of Lactopeptine.—Editorial in *Jour. Indiana State M. A.*, May 15, 1913, p. 219.

THE "HUMAN AQUARIUM."

Sternberg describes his examination of a circus freak who is able to drink up to seven quarts of water at a time and expel it through his mouth at will without any evidence of nausea. He also swallows live frogs and fishes and expels them in the same way. His father and grandfather had this same faculty of being able to ingest and expel large quantities of fluid at will. Sternberg noticed that the young man swallowed the ten frogs first and

also expelled them first. Roentgenoscopy showed the stomach apparently normal in every respect.—*Jour, A. M. A.,* March 29, 1913, p. 1037.

MANUFACTURE AND USES OF DENATURED ALCOHOL TO BE STUDIED.

The Bureau of Foreign and Domestic Commerce, Department of Commerce, has arranged for a report by a special agent upon the use of tax-free alcohol for industrial purposes (denatured alcohol) in the principal countries of Europe.

The Bureau published last December a report on this subject made up from letters received from consuls in various foreign countries, but it is considered desirable at this time to have a special report by an agent thoroughly familiar with the manufacture and applications of industrial alcohol that will cover the field of the countries which make the most extensive and intelligent use of the privilege of tax-free alcohol.

The report will be based upon a personal investigation by the agent of the Bureau of the sources, manufacture, governmental inspection and encouragement, and all matters of interest in connection with denatured alcohol from the standpoint of its production, together with its various applications in different lines of industry, the cost to consumers, its relative merits as a liquid fuel for internal combustion engines, etc. Conditions will be studied in Great Britain, France, Germany, and the other principal countries of Europe. The investigation will be made during the coming summer, and the report published in the fall.

THE CONSTITUTION OF CYTISINE, THE ALKALOID OF CYTISUS LABURNUM.

The poisonous alkaloid of the common laburnum was first isolated in a pure form by Husemann and Marmé, who gave it the chemical formula $C_{20}H_{27}ON_3$. Later on the true composition of the alkaloid was shown by Fartheil to be $C_{11}H_{14}ON_2$, and this was further confirmed by Buchka and Magelhaës as well as subsequent workers. Dale and Laidlaw have reported that in its physiological action it closely resembles that of nicotine.

M. Freund elucidated the following main facts as a result of a chemical examination of this alkaloid by treatment with HI and phosphorus at a temperature of 230°:

(*a*) Cytisoline, $C_{11}H_{11}ON$, a feebly basic, crystalline solid, melting when pure at 198°.

(*b*) β-Cytisolidine, $C_{11}H_{15}N$, a basic oil, yielding a crystalline picrate (m.p. 229°) and platinichloride (m.p. 234°).

(*c*) A mixture of hydrocarbons melting at 185–230°.

(*d*) Ammonia.

Later Freund found that on electrolytic reduction, cytisine was changed into a base, tetrahydrodeoxycytisine. The action of hydriodic acid seemed to offer the only hope for determining the constitution of cytisine. Many attempts were made to get some product of oxidation from the alkaloid which might throw some light on the problem of its constitution. It is readily attacked by oxidizing agents; such as potassium permanganate and chromic acid, but, however the conditions are varied, no pure product can be isolated except oxalic acid. Attempts to decompose cytisine by the action of acids or alkalies at high temperature proved unavailing. Cytisine is stable to a remarkable degree towards these reagents. The experiments of Freund were very carefully repeated by Ewins, who gives in detail his work on the subject and seems to think that the constitution of this alkaloid remains an open question (A. J. Ewins, B.Sc. *Transactions of the Chemical Society,* Vol. 103, 1913. London.)

JOHN K. THUM.

THE CONSTITUTION AND SYNTHESIS OF DAMASCENINE, THE ALKALOID OF NIGELLA DAMASCENA.

The literature relating to this alkaloid is briefly reviewed and the main facts brought out. Schneider (Pharm. Centr.-h., 1890, 31, 173) was the first to isolate it from the seeds of *Nigella damascena.* He described it as a crystalline solid, m. p. 27°, with the composition $C_{10}H_{15}O_3N$. Subsequently this was shown to be substantially correct, the formula really being $C_{10}H_{13}O_3N$.

The constitution of damasceninic acid, easily formed from damascenine, was shown by Keller to be 2-methylamino-3-methoxybenzoic acid. He unsuccessfully attempted its synthesis.

Ewins gives his method of extracting the alkaloid from the seeds by the shaking out process, using light petroleum. The alkaloid and its salts agreed absolutely with the synthetic product and its salts.

All the work done in building up this synthetic is carefully detailed in a most interesting manner.

Briefly it consists of converting m-hydroxybenzoic acid into m-methoxybenzoic acid by methyl sulphate and potassium hydroxide. This acid on nitration under suitable conditions gives a mixture of nitro-derivatives, from which the required 2 nitro-3-methoxybenzoic acid is isolated without difficulty. This on reduction yields 2 amino-3-methoxybenzoic acid, which on treatment with methyl iodide yields the hydriodide of 2 methylamino-3-methoxybenzioc acid. This salt was converted into the corresponding hydrochloride, which was found to be identical with the hydrochloride of damasceninic acid. The acid on esterifying by Fisher's method gave a methyl ester, which proved to be identical with the natural alkaloid damascenine.

The steps in the synthesis are shown by the following scheme:

m–Hydroxybenzoic acid.
↓
m–Methoxybenzoic acid.
↓
2 Nitro–3–methoxybenzoic acid.
↓
2 Amino–3–methoxybenzoic acid.
↓
2 Methylamino–3–methoxybenzoic acid.
↓
Methyl 2–methylamino–3–methoxybenzoate (damascenine).

(A. J. Ewins in *Transactions of the Chemical Society,* Vol. 101, 1912. London.)

JOHN K. THUM.

PEPPER.

Pepper of commerce is the product of *Piper nigrum,* a trailing or climbing vine of the East Indies.

Both the white and black pepper are from the same plant, in the case of the white kind, the rind or outer covering is removed by maceration, drying white. Chinese pepper planters obtain pepper for their own use in a very singular manner. Certain tropical birds are very fond of eating the "red" pepper berries and appear to discriminate, selecting only the very best. These are undigested and voided by the birds, the "garden" coolies are instructed to

gather all obtainable, it being most highly prized and quite unobtainable in commerce; in fact, to receive a gift of this from a Chinese towkay is considered to be a mark of very great esteem. In cultivation a "pepper garden" somewhat resembles an hop garden, the vines are planted on hillocks and are trained around poles and look very pretty with their harvest of green, red, and black berries.

From a letter by Ernest Jenkins, of Kew Gardens, to the writer.

C. S. Braddock, Jr.

VOLATILE ANTISEPTICS AND SOIL ORGANISMS.

In an article on "The Effect of Toluol and Carbon Disulphide on the Micro-flora and -fauna of the Soil," P. L. Gainey (Missouri Botanical Garden, Twenty-third Report, 1912), draws the following conclusions:

1. That small quantities of carbon disulphide, toluol, and chloroform, such as have been used practically and experimentally, when applied to the soils studied, exert a stimulative rather than a diminishing effect upon the total number of bacteria present.

2. That an application of such quantities of carbon disulphide and toluol does not have an appreciable effect upon the number of types of protozoa present in such soils as have been studied.

3. That a very marked increase in yield may be noted following such an application when no evident change occurs in total number of bacteria present.

4. That, in the light of the recent work of Koch, Eforoo, Goodsey, Fred, and others, with results presented in this paper, the theory advanced by Russell and Hutchinson to account for the increased yield following the application of such chemicals, appears not tenable for general application.

THE SOURCE OF SIAM BENZOIN.

The lack of information as to the source of Siam benzoin has been pointed out at various times in the *Pharmaceutical Journal* by Mr. E. M. Holmes, and in response to his application for assistance to trace the origin of the product Dr. Kerr was communicated with on the subject. We are much indebted to Dr. Kerr for his kind

reply to our enquiry from which we have extracted the following interesting information.

The *Styrax* tree which grows on Doi Sootep and which is fairly common at 600 to 1200 M. altitude in evergreen jungles particularly in that type of forest where *Quercus Junghuhnii* predominates and where the soil consists of a stiff red clay overlain by a thick layer of humus, was, from flowering material only, believed to be *S. Benzoin* (*Kew Bull.*, 1911, p. 409). The receipt of fruiting specimens showed, however, that it was not *S. Benzoin* but a new species closely allied to *S. suberifolius* and since described as *S. benzoides* (*Kew Bull.*, 1912, p. 267). *S. benzoides*, on Doi Sootep, grows rapidly and attains a height of 12–15 m. and a girth of about 9 dm. but most of the trees are smaller though in other parts larger trees are reported. Several Kamus, natives of the Luang Prabang region from which most of the gum comes, have, without a leading question, identified the Doi Sootep tree as ton kum yan, kum yan being the Lao and Siamese name for gum benzoin. It must be admitted that small specific differences might not be noted by the natives though they are often acute observers of such points particularly where economic plants are concerned.

Dr. Kerr's belief that this tree is the source of the Siamese gum benzoin has been confirmed by the receipt at Kew of a small sample of the gum collected from the Doi Sootep trees which in smell, taste and fumes is identical with commercial Siamese gum benzoin. Though the gum is only casually collected in the Chiengmai district yet nearly every tree examined on Doi Sootep had been notched and in some cases completely felled. In the majority of cases the cuts were very old and on most trees no gum at all was observed but on a few there was a small incrustation of gum along the cuts. The largest piece of gum obtained weighed about 2.5 grammes and was found in a hole made by some wood-borer. It was a homogeneous, transparent, pale amber piece with the characteristic odor of Siam benzoin.

The principal method of collecting the gum is by making V-shaped incisions through the bark. The gum runs slowly into bamboo joints placed at the bottom of the V, and is not collected until a few weeks after the incision is made. This is generally done during the hot season. Gum is also frequently found in holes made by wood-borers and sometimes on or in the ground at the foot of the trunk. The quality of the gum is the same by whatever

method it is collected. Whether any particular tree will yield gum or not can only be ascertained by tapping, as only the larger trees and not even all of them yield gum.

None of the gum obtained near Chiengmai is exported, but nearly all of it is used locally, mixed with pig's fat, as an application for the hair. Most of the gum which reaches Chiengmai is brought there by the Kamus during the cold season from the Luang Prabang region to the East of the Mê Kong. A native merchant buys it and ships it to Bangkok. This merchant estimates his yearly purchases at 5 sens (approximately 10 cwt.), but for the last two years the quantity has been less, because, he says, it no longer pays the Kamus to collect it and bring it down. Although the merchant had heard that the tree grew on Doi Sootep he had never bought gum from any district but Luang Prabang.

Gum benzoin is also brought to Korat in Lower Siam but no information as to its source is available.—*Kew Bulletin.* Reprinted in *Bangkok Times Weekly Mail.*

CHARLES S. BRADDOCK, JR.

BOOK REVIEW.

PROCEEDINGS OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, including the report on the progress of pharmacy to January 1, 1912. Also the constitution, by-laws and roll of members. Scio, Ohio: Published by the American Pharmaceutical Association, 1912.

This long expected volume has finally reached the members of the American Pharmaceutical Association and despite the fact that the title is somewhat of a misnomer because the book contains no record of the proceedings at the annual meeting of the American Pharmaceutical Association, the volume will nevertheless be generally welcome because of the 524 pages devoted to the report on the progress of pharmacy from July 1, 1910, to December 31, 1911. This report is prefaced by an introductory in which the venerable reporter on the progress of pharmacy records the origin and subsequent development of these reports and expresses the hope that the proposed publication of selected abstracts in the Journal of the Association will disarm much of the criticism formerly made regarding delay in publication of the annual volume. In addition to the proposed publication of selected abstracts in the journal of the

constitution and by-laws of the American Pharmaceutical Association, are a geographical roll of members, an alphabetical list of members and a well arranged index of 34 double column pages that will serve to make the content of the volume of permanent value to pharmacists who are interested in the professional side of their calling. The receipt of this volume will no doubt reawaken in the minds of many, and let us hope the majority of the members of the American Pharmaceutical Association, the hope that the recent decision, of the Councils of the Association, to discontinue the annual volume will be reconsidered and that ways and means will be found to continue the publication of the Report of the Progress of Pharmacy in the form of a bound, separately indexed volume in keeping with the one now before us.

M. I. W.

OBITUARIES.

John W. Ridpath, son of Robt. Ridpath and Eleanor Blair, was born in Upper Onslow, Colechester County, Nova Scotia, Oct. 1st, 1840. His father, a ship carpenter, was drowned on July 19, 1841, while trying to save the life of a fellow workman.

During the fall of 1864, Mr. Ridpath visited his home in Nova Scotia, stopping at Boston on his way. Upon returning to the United States he took up his residence at Jenkintown, purchasing the painting business of William Pearson. He took out his naturalization papers on Oct. 13th, 1868, voting for the first time in Abington Township, now Jenkintown, on Oct. 12th, 1869.

Finding the work detrimental to his health, in the fall of 1870 he discontinued the business of painting and entered the drug business, which he continued until April 8th, 1892. He was made a member of the Philadelphia College of Pharmacy, Aug. 5th, 1870, and of the Pennsylvania Pharmaceutical Association, April 23rd, 1880.

His membership in the Franklin Institute dates from March 10th, 1882, from which time he has taken an active part in the work of the Institute, lecturing before that body and many other prominent societies, and public and private schools of the lower end of Montgomery County.

On April 25th, 1889, Mr. Ridpath was elected Secretary of

the Jenkintown Water Company and on Jan. 7th, 1890, Manager of the same.

He has served the public in the following offices: Borough Auditor, three years, beginning 1875; Board of Health, from its organization in 1885 until 1887; Justice of the Peace, five years, taking the oath of office on April 27th, 1888.

He has been connected in an official capacity with the Cheltenham and Willow Grove Turnpike Company since Nov. 8th, 1886, when he was elected Manager and Secretary; also with the Doylestown and Willow Grove Turnpike Road Company and the Hatboro and Warminster Turnpike Road Company, under the direction of the Philadelphia Rapid Transit Company.

At the time of his death, he was Secretary of the Jenkintown Lyceum Association, of which body he has been a member since Sept. 19th, 1876. He was a charter member of Pioneer Fire Company No. 1, of Jenkintown; also a charter member of Jenkintown Lodge, No. 400, F. & A. M.; a member of Abington R. A. Chapter No. 245; President of the Board of Directors of the Abington Library Society; a member of the National Geographical Society; of the Franklin Institute of Pennsylvania; Life Member of the Philadelphia College of Pharmacy; member of the American Good Roads Association; of Jenkintown Lodge No. 476, K. of P.; active member of the Bucks County Historical Society; Superintendent and Treasurer of Cheltenham and Willow Grove Turnpike Company, of Hatboro and Warmister Turnpike Road Company and of the Doylestown and Willow Grove Turnpike Road Company.

Mr. Ridpath was elected corresponding member of the Adjunct Montgomery County Medical Society on May 8th, 1885, and at the time of his death was one of the two living original members. His fame as a local historian was known throughout the Counties of Montgomery, Bucks, and Philadelphia, many of his articles having appeared in various magazines. Among them are "The Early History of Jenkintown," "Amateur Photographic Failures," "Free Masonry in Jenkintown," "History of Friendship Lodge, No. 400," and "Early Ridpaths in Scotland." He edited the first newspaper ever published in the Borough of Jenkintown, "The Pestle."

He is survived by a widow, two sons, and three daughters.

Horace W. Estlack, engaged in the retail drug business at 1233 South 17th Street, died March 8, 1913, from pneumonia after an illness of one week. His ancestors were members of the Society of Friends. He served part of his apprenticeship with his father, Thomas A. Estlack, a graduate of our college of the class of '44, who owned a store at 18th and Market Street. He completed his apprenticeship at the store of Mr. Amos Yarnall, whose store was located at 15th and Market Street. Mr. Estlack graduated in 1868, his graduating thesis being on Podophyllum. He conducted a business for himself at 16th and Race Street in 1872. Two years later he opened a store at 1233 South 17th Street which he conducted until the time of his death. He joined the college in 1893. He led a very active life, had a number of outside interests and was entrusted by his fellows with positions requiring confidence and which he faithfully discharged.

PENNSYLVANIA PHARMACEUTICAL ASSOCIATION.

The annual meeting of the Pennsylvania Pharmaceutical Association was attended by a large number of pharmacists, representing all phases of the profession and trade. Great enthusiasm prevailed when it was announced by John C. Wallace, Chairman of the Committee on Legislation, that house bill 532 for the restriction of the sale of habit-forming drugs had passed the Senate and was before the Governor. This bill was framed by L. L. Walton of Williamsport and received the support of the State Association which, with the Philadelphia Association of Retail Druggists, has been making every effort to secure its passage. It prohibits the indiscriminate sale of such drugs as opium, morphine, heroin, and codeine except upon the prescription of a physician, dentist or veterinary, but does not prohibit the public from getting legitimate preparations, containing certain specified minimum quantities of these drugs. The bill conforms to a national measure introduced in Congress by Representative Hartyson of New York. The Association forwarded a resolution to Governor Tener urging him to sign the bill.

The following officers were elected: President, Richard L. Lackey; First Vice President, Charles R. Rhodes; Second Vice President, George J. Durbin; Secretary, Edgar F. Heffner; Assistant Secretary, Lewis H. Davis; Treasurer, H. E. Gleim.